REMARKS

In view of the above amendments and the following remarks, reconsideration of the outstanding office action is respectfully requested. Pursuant to 37 CFR § 1.121, attached as Appendix A is a Version With Markings to Show Changes Made.

Protein kinases are a large class of enzymes which catalyze the transfer of the γ-phosphate from ATP to the hydroxyl group on the side chain of Ser/Thr or Tyr in proteins and peptides and are intimately involved in the control of various important cell functions, perhaps most notably: signal transduction, differentiation and proliferation. There are estimated to be about 2,000 distinct protein kinases in the human body, and although each of these phosphorylate particular protein/peptide substrates, they all bind the same second substrate ATP in a highly conserved pocket.

Inhibitors of various known protein kinases could have a variety of therapeutic applications provided sufficient selectivity, and acceptable *in vivo* pharmacological properties, can be incorporated into such inhibitors. Perhaps the most promising potential therapeutic use for protein kinase inhibitors is as anti-cancer agents. This potential application for protein tyrosine kinase ("PTK") inhibitors has been highlighted in many recent reviews. The foundation for this application is based partly upon the fact that about 50% of the known oncogene products are PTKs and their kinase activity has been shown to lead to cell transformation.

The PTKs can be classified into two categories, the membrane receptor PTKs (e.g. growth factor receptor PTKs) and the non-receptor PTKs (e.g. the src family of proto-oncogene products). There are at least 9 members of the src family of non-receptor PTK's with $pp60^{c\text{-}src}$ (hereafter referred to simply as "src") being the prototype PTK of the family wherein the ca. 300 amino acid catalytic domains are highly conserved. The hyperactivation of src has been reported in and number of human cancers, including those of the colon, breast, lung, bladder, and skin, as well as in gastric cancer, hairy cell leukemia, and neuroblastoma. Overstimulated cell proliferation signals from transmembrane receptors (e.g. EGFR and p185HER2/Neu) to the cell interior also appears to pass through src. Consequently, it has recently been proposed that src is a universal target for cancer therapy because its hyperactivation (without mutation) is involved in tumor initiation, progression and metastasis for many important human tumor types.

In view of the large, and growing, potential for inhibitors of various protein kinases, a variety of approaches to obtaining useful inhibitors is needed. The status of the discovery of PTK inhibitors has been extensively reviewed. Random screening efforts have been successful in identifying non-peptide protein kinase inhibitors but the vast majority of these bind in the highly conserved ATP binding site. A notable recent example of such non-peptide, ATP-competitive, inhibitors are the 4-anilinoquinazolines, and analogs, which were shown to be effective against the epidermal growth factor receptor PTK (EGFRTK). Although this class of inhibitors was reported to be selective for the EGFR PTK vs. six other PTKs (including src) it is unknown what their effect is on most of the remaining 2,000 protein kinases that all bind ATP as well as a large number of other ATP, ADP, GTP, GDP, etc. utilizing proteins in the body. Therefore, potential side effects from PTK inhibitor drugs that mimic ATP, which might only be discovered after expensive animal toxicity studies or human clinical trials, are still a serious concern. Also, although this class of compounds was a nice discovery and is undergoing further exploration, they do not provide a rational and general solution to obtaining non-peptide inhibitors for any desired PTK, e.g. in this case src. The risk of insufficient specificity *in vivo* with ATP-competitive PTK inhibitors has also been noted by others, along with the inherent three order of magnitude reduction in potency these inhibitors display when competing with the mM levels of intracellular ATP rather than the μM levels used in the isolated enzyme assays.

An older, and more extensively studied, class of non-peptide PTK inhibitors is erbstatin and the related tyrphostins. This class of inhibitors are active against the receptor PTKs and their mode of inhibition is complex but does not appear to involve binding in the peptide substrate specificity site regions of the active site. Furthermore, they are inactive against the isolated PTK when the *unnatural* assay metal Mn^{2+} is replaced with the *natural* Mg^{2+}, are chemically unstable, and are known to be cytotoxic to normal and neoplastic cells by crosslinking proteins as well as inhibit cell growth by disrupting mitochondria rather than PTK inhibition.

An important contribution to the protein kinase field has been the x-ray structural work with the serine kinase cAMP-dependent protein kinase ("PKA") bound to the 20-residue peptide derived from the heat stable inhibitor protein, PKI(5-24), and Mg_2ATP. This structural work is particularly valuable because PKA is considered to be a prototype for the entire family of protein kinases since they have evolved from a single ancestral protein kinase. Sequence alignments of PKA with other serine and tyrosine kinases have identified a

conserved catalytic core of about 260 residues and 11 highly conserved residues within this core. Two highly conserved residues of particular note for the work proposed herein are the general base Asp-166 which is proposed to interact with the substrate OH and the positively charged residue, Lys-168 for serine kinases and an Arg for tyrosine kinases, which is proposed to interact with the γ-phosphate of ATP to help catalyze transfer of this phosphate. Two additional important PKA crystal structures have been reported, one for the ternary PKA:ADP:PKI(5-24) complex wherein the PKI Ala 21 has been replaced with Ser (thereby becoming a substrate), and one for the binary PKA:PKI(5-24) complex wherein the PKI Ala 21 has been replaced with phosphoserine (an end product inhibitor). The ternary complex shows the serine OH donating a H-bond to Asp-166 and accepting a H-bond from the side chain of Lys 168. The binary complex shows the phosphate group of phosphoserine forming a salt bridge with the Lys-168 side chain and within H-bonding distance of the Asp-166 carboxyl group. These structures support the earlier proposed roles for Asp-166 and Lys-168 in the catalytic mechanism.

The x-ray structures of PKA show that the enzyme consists of two lobes wherein the smaller lobe binds ATP and the larger lobe the peptide substrate. Catalysis occurs at the cleft between the lobes. The crystallographic and solution structural studies with PKA have indicated that the enzyme undergoes major conformational changes from an "open" form to the "closed" catalytically active form as it binds the substrates. These conformational changes are presumed to involve the closing of the cleft between the two lobes as the substrates bind bringing the γ-phosphate of ATP and the Ser OH in closer proximity for direct transfer of the phosphate.

However, the inhibitors of protein kinases still lack the specificity and potency desired for therapeutic use. Due to the key roles played by protein kinases in a number of different diseases, including cancer, psoriasis, arthrosclerosis, and their role in regulating immune system activity, inhibitors of specific protein kinases are needed. The present invention provides a novel approach for designing protein kinase inhibitors, which are more potent as well as being more specific for the targeted pathways.

The rejection of claims 1-7, 9-13, and 18-20 under 35 U.S.C. § 112, second paragraph, for indefiniteness is respectfully traversed in view of the above amendments and the following remarks.

With regard to the rejection of claims 1-7, 9-13, and 20, as used herein, the term "module" is defined to include a single molecular entity or a collection of functional

groups. Support for this definition is found at page 36, lines 8-11 of the specification, which sets forth that "[p]referred first modules have a functional group . . . The compounds of the present invention may have two or more functional groups within the first module. More preferred modules are boronic acid groups, a hydroxyl group, or an amide group." In addition, the first module (i.e., M_1) is defined as "a selection of validated functionalities for binding to the conserved catalytic residues" and the second module (i.e., M_2) is defined as "a selection of non-peptide scaffolds for PTK's" in Figure 1.

With regard to the rejection of claim 1 for the language "non-peptide scaffold," as noted at page 4, item E of the outstanding office action, the term "non-peptide scaffold" includes molecules with peptide bonds, so long as a part of the molecule is not a peptide.

With regard to the rejection of claim 1 for the language "a first module having one or more functional groups for binding to catalytic residues of the protein kinase," applicants have amended claim 1 to recite that each first module has "one or more functional groups each capable of covalently or non-covalently binding to catalytic residues of the protein kinase." Thus, each functional group of the first module is capable of reversible or irreversible bond formation, either covalently or non-covalently, to catalytic residues of the protein kinase when the protein kinase and the first module are combined under conditions effective for such binding.

With regard to the rejection of claim 18 for the language "protein serine kinase," as noted at page 5, item J of the outstanding office action, the term "protein serine kinase" is equivalent to the term "serine-threonine kinase."

With regard to the rejection of claim 20 for the language "specificity side chain elements," specificity side chain elements are side chains which will bind in unique binding pockets for individual protein kinases. Such a definition is supported by Figure 1 of the present application, which shows that specificity side chain elements (S_n) bind to substrate specificity sites of protein kinases.

Accordingly, the rejection of claims 1-7, 9-13, and 18-20 for indefiniteness is improper and should be withdrawn.

The rejection of claims 1-4, 7, 9, 12, 15, and 18 under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 6,011,175 to Sebti et al. and U.S. Patent No. 5,705,585 to Hogan, Jr. ("Hogan") is respectfully traversed in view of the above amendments incorporating the limitations of claim 10 into claim 1.

The rejection of claims 1-9, 12-18, 20, and 22 under 35 U.S.C. § 103(a) as being unpatentable over Hogan, Lawrence et al., "Protein Kinase Inhibitor: The Tyrosine-Specific Protein Kinases," Pharmacol. Ther., 77:81-114 (1998), and U.S. Patent No. 5,552,534 to Hirschmann et al. is respectfully traversed in view of the above amendments incorporating the limitations of claim 10 into claim 1.

In view of the all of the foregoing, applicants submit that this case is in condition for allowance and such allowance is earnestly solicited.

Respectfully submitted,

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Appendix A

Version With Markings to Show Changes Made

In reference to the amendments made herein to claims 1-7, 13, 19, and 20, additions appear as underlined text, while deletions appear as bracketed text, as indicated below:

In The Claims:

1. (Amended) A method for identifying inhibitors of protein kinases comprising:

[providing a] identifying at least one first module having [a] one or more functional groups [for] each capable of covalently or non-covalently binding to catalytic residues of the protein kinase;

[combining] covalently attaching the at least one first module to [with a] at least one second module which provides a non-peptide scaffold, wherein the at least one second module comprises an indole, to form one or more combinations of the first and second modules; [and]

screening the one or more combinations of the first and second modules for protein kinase inhibition; and

selecting combinations of the first and second modules which inhibit protein kinase activity.

2. (Amended) The method according to claim 1, wherein said [providing a] identifying at least one first module comprises:

covalently attaching the at least one first module to a peptide scaffold;

identifying one or more functional groups on the first module which preferentially bind to catalytic residues of the protein kinase; and wherein said [combining] covalently attaching the at least one first module [with the] to at least one second module comprises:

substituting the at least one second module for the peptide scaffold.

3. (Amended) The method according to claim 1, wherein the at least one first module comprises a functional group selected from the group consisting of boronic

acid, a hydroxyl group, phosphonic acid, sulfamic acid, a guanidino group, carboxylic acid, an aldehyde, an amide, and hydroxymethylphosphonic acid.

4. (Amended) The method according to claim 3, wherein the at least one first module comprises two or more functional groups.

5. (Amended) The method according to claim 3, wherein the at least one first module comprises a boronic acid group.

6. (Amended) The method according to claim 3, wherein the at least one first module comprises a hydroxyl group.

7. (Amended) The method according to claim 3, wherein the at least one first module comprises [a] an amide group.

13. (Amended) The method according to claim 1, wherein the at least one first module further comprises a linear chain comprising between one and three carbon atoms which links the at least one first module to the at least one second module.

19. (Amended) The method according to claim [15] 18, wherein the protein serine kinase is selected from the group consisting of MAP kinase, protein kinase C, and CDK kinase.

20. (Amended) The method according to claim 1, further comprising:

[adding] covalently attaching one or more specificity side chain elements to the [combination] one or more combinations of the first and second modules.